

GLUCONEOGENESIS

OBJECTIVES

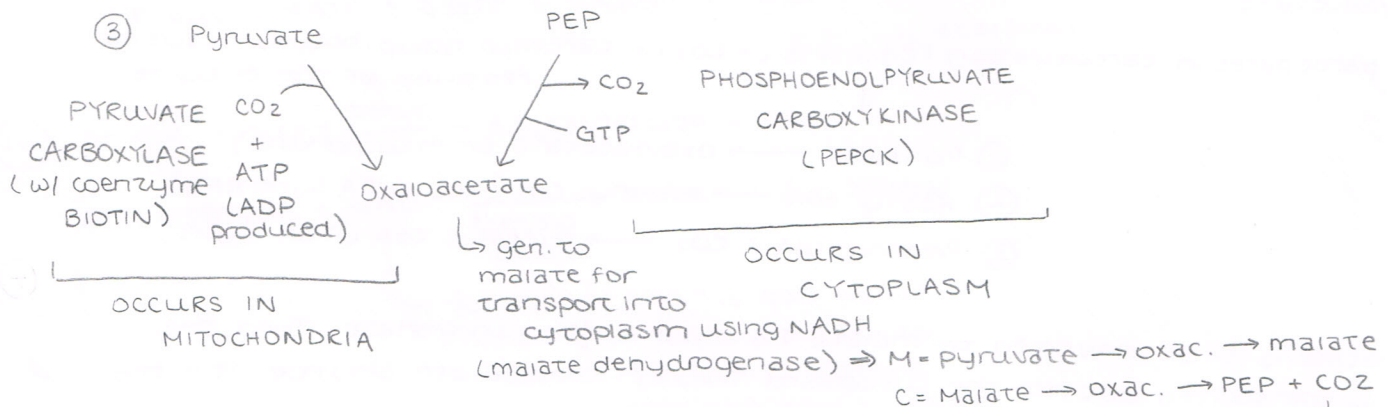
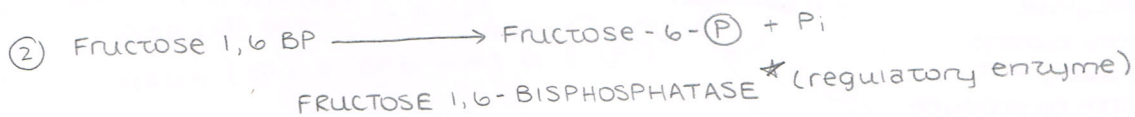
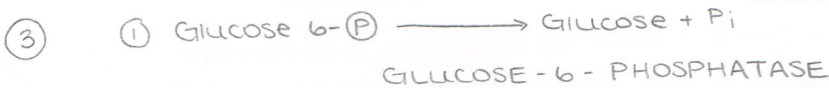
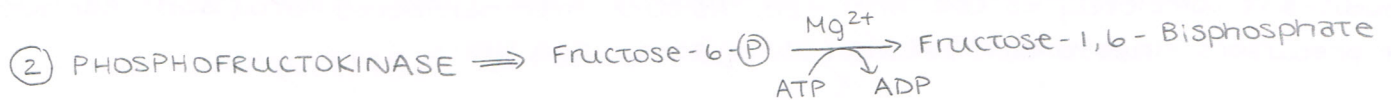
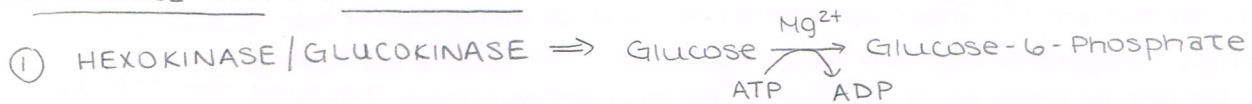
- ① Lactate is converted to Pyruvate and then undergoes a series of reverse glycolytic steps to synthesize glucose.

Gluconeogenesis occurs primarily in the liver and kidney.

Mitochondria and Cytoplasm are the parts of the cell that participate in gluconeogenesis.

COMMON PRECURSORS = Lactate (comes from exercising muscles, anaerobic glycolysis in RBCs)
 Pyruvate + precursors (Glycolysis) + Pentoses + other Hexoses
 Amino Acids (Proteins)
 Glycerol (triglycerides)
 Propionate (odd-numbered fatty acids)

② IRREVERSIBLE STEPS OF GLYCOLYSIS



\hookrightarrow this being liberated drives rxn. forward

④ GLUCONEOGENESIS

Pyruvate Carboxylase adds CO_2 to Pyruvate to produce Oxaloacetate in the mitochondria

ANAPLEROSIS

Pyruvate Carboxylase produces oxaloacetate (lack) when stimulated by Acetyl CoA (needed for essential TCA intermediate) Also, ATP is needed.

* Pyruvate Carboxylase is a regulatory enzyme. Acetyl CoA is a (+) modulator. Biotin is required as a coenzyme.

CONVERSION OF PYRUVATE \longrightarrow PHOSPHOENOLPYRUVATE

- ① Pyruvate + CO₂ + ATP $\xrightarrow[\text{Acetyl CoA}]{\text{PYRUV. CARBOXYLASE (coenzyme = biotin)}}$ Oxaloacetate + ADP + P_i
- ↳ doesn't go fwd. w/o this
(fueled by β -oxidation)
↳ ATP liberated drives gluconeogenesis
- ② Oxaloacetate + NADH + H⁺ $\xrightarrow{\text{Malate Dehydrogenase}}$ Malate + NAD⁺
- ↳ transp. out to cytoplasm
- ③ Malate + NAD⁺ $\xrightarrow{\text{Malate Dehydrogenase}}$ Oxaloacetate + NADH + H⁺
- ④ Oxaloacetate + GTP $\xrightarrow[\text{PEPCK}]{\text{Acetyl CoA, Mg}^{2+}}$ Phosphoenolpyruvate + CO₂ + GDP
- ⑤ Acetyl CoA cannot be used as a precursor for gluconeogenesis because the TCA cycle oxidizes it completely to CO₂ and H₂O. As such, even numbered fatty acids cannot be precursors since they're catabolized to acetyl CoA units.
- ⑥ Acetyl CoA is a (+) modulator of Pyruvate carboxylase. Without it, the enzyme would not be able to bypass the conversion of pyruvate to phosphoenolpyruvate.

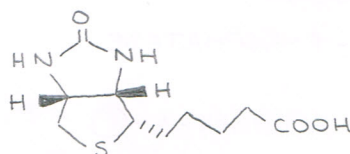
IN MITOCHONDRIA

OUTSIDE OF MITOCHONDRIA

⑦ ROLE OF BIOTIN IN GLUCONEOGENESIS

- acts as a coenzyme of carboxylation reactions
- w/ pyruvate carboxylase, P from ATP activates biotin's imidazole ring allowing PC to add CO₂ to pyruvate to produce oxaloacetate.

STRUCTURE OF BIOTIN



NATURE OF BIOTIN-ENZYME LINKAGE

Bound in an amide linkage to a lysine residue of an enzyme

★ Biotin participates in carboxylation reactions (+ CO₂) = carboxyl group bound to lysine residues of the enzyme



- ① Pyruvate \longrightarrow Oxaloacetate (in mitochondria)
- ② Acetyl CoA \longrightarrow Malonyl CoA (ACC in FA synthesis)
- ③ Propionyl CoA + CO₂ \longrightarrow Succinyl CoA (TCA cycle)

- ⑧ Oxaloacetate is first converted to malate via malate dehydrogenase. Then, the malate is transported out into the cytoplasm through the malate shuttle. It is then converted back to malate by malate dehydrogenase.

- ⑨ Glycerol can be converted to glucose via glycerol kinase
- ↳ 3C (Glycerol) $\xrightarrow{\text{GLYCEROL KINASE}}$ Glycerol-3-P $\xrightarrow{\text{GLYCEROL-3-P DEHYDROG.}}$ DHAP
- ↳ FIRST GLYCOLYTIC INTERMEDIATE

Even-numbered fatty acids cannot form glucose because they are catabolized to acetyl CoA units that are fully oxidized to 2CO₂ and H₂O in the TCA cycle.

The muscles and brain can't synthesize glucose because they lack the enzyme, GLUCOSE-6-PHOSPHATASE. This way, the organs can use glucose solely for NRG (none will be exported to the liver).

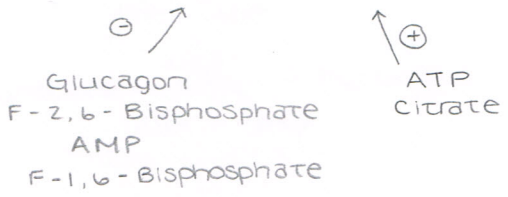
11 Lactate (from muscles) is converted in the liver. Alanine is converted primarily in the liver; sometimes in the kidney.

Both are converted to pyruvate \Rightarrow eventually synthesizes new glucose

12 For triglyceride synthesis, glycerol is needed for the backbone. However, in adipose tissue, glycerol kinase (enzyme) is not present so glycerol can't be phosphorylated so DHAP won't be synthesized. Therefore, glucose is needed for synthesizing DHAP which can be converted to glycerol-3-phosphate.

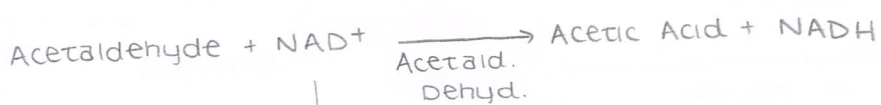
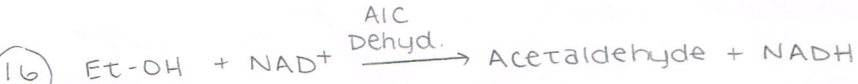
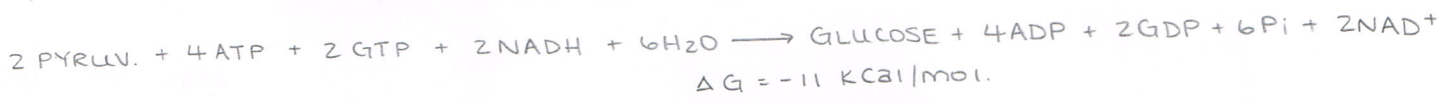
13 Amino Acids can be converted to TCA intermediates by removal of the amino group. Eventually, all of the TCA intermediates will generate oxaloacetate. This can be transported out of the mitochondria and converted to malate (malate shuttle) which gives rise to PEP via PEPCK thus proceeding w/ the gluconeogenic pathway.

14 PRIMARY CONTROL STEP: Acetyl CoA (+) modulates pyruvate carboxylase
SECONDARY CONTROL STEP: regulation of Fructose-1,6-Bisphosphatase



15 Remember = need 2 pyruvate to make 1 glucose

6 ATP equivalents needed! { 4 ATP (2 @ pyruv. \rightarrow oxalo. and 2 @ 3-PG \rightarrow 1,3-BPG)
 2 GTP (@ oxalo. \rightarrow PEP)
 2 NADH (@ 1,3-BPG \rightarrow G-3-P)



\rightarrow depletion of NAD^+ is bad b/c it's necessary to convert lactate to pyruvate. Inhibition of lactate dehydrogenase can lead to lactic acidosis, hypoglycemia or possible coma.